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**Health and Environmental Effects
Profile for Isopropalin**

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR ISOPROPALIN

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16. ABSTRACT The Health and Environmental Effects Profile for <u>isopropalin</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>Isopropalin</u> has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for <u>isopropalin</u> is 5.6×10^{-2} (mg/kg bw/day) for oral exposure. 1056		
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA docket.

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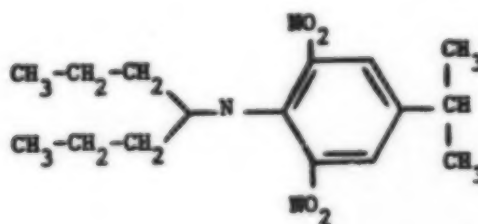
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
K _{oc}	Soil adsorption coefficient
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Isopropalin is the common name for 4-isopropyl-2,6-dinitro-N,N-dipropylaniline. Current Chemical Abstract usage is 4-(1-methylethyl)-2,6-dinitro-N,N-dipropylbenzenamine and was formerly 2,6-dinitro-N,N-dipropylcumidine. Another chemical synonym is 2,6-dinitro-N,N-dipropyl-p-isopropylaniline. Isopropalin was introduced in 1969 by Eli Lilly and Company under the code number "EL-179" and the currently used trade name "Paarlan" (emulsifiable concentrate) (BCPC, 1977; U.S. EPA, 1981). Paarlan emulsifiable concentrate contains 68.6% isopropalin (U.S. EPA, 1981). The structural and molecular formulae for isopropalin are as follows:



Molecular formula: $C_{15}H_{23}N_3O_4$

Molecular weight: 309.4

The Chemical Abstract Service (CAS) Registry number is 33820-53-0.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Isopropalin is an orange-red liquid oil at ordinary temperatures (BCPC, 1977; WSSA, 1979). Selected physical properties are listed below.

Vapor pressure:	1.45×10^{-5} mm Hg at 30°C (WSSA, 1979)
Water solubility:	0.1 mg/l (BCPC, 1977) 0.11 ppm (Kenaga, 1980)
K_{oc} :	
experimental	75,250 (Kenaga, 1980)
calculated	14,700 (Kenaga, 1980)

BCF:

calculated from water
solubility:
calculated from K_{oc}

2150 (Kenaga, 1980)
7500 (Kenaga, 1980)

Isopropalin is readily soluble in organic solvents such as acetone, acetonitrile, benzene, chloroform, ethyl ether, hexane and methanol (WSSA, 1979). It is susceptible to decomposition by UV irradiation but otherwise stable at ordinary conditions (BCPC, 1977). It decomposes at elevated temperatures (U.S. EPA, 1981).

1.3. PRODUCTION DATA

Isopropalin is made by the reaction of 1-chloro-4-isopropyl-2,6-dinitrobenzene with dipropylamine (BCPC, 1977).

Eli Lilly and Company manufacture isopropalin in Lafayette, Indiana (SRI, 1983); Ciba-Geigy Corp. is also listed as a manufacturer (USITC, 1983). Approximately 0.4-0.5 million pounds of isopropalin are produced annually (U.S. EPA, 1981).

1.4. USE DATA

Isopropalin is used as a preemergence herbicide to control annual grasses and broadleaf weeds (WSSA, 1979; U.S. EPA, 1981). It is used almost exclusively on tobacco fields. Isopropalin is applied by spray nozzles located 18 inches above the soil at rates of 1.5 to 2.0 pounds of active ingredient per acre. Incorporation into the soil is done immediately after application.

In both 1976 and 1982, 0.3 million pounds of isopropalin were used in American tobacco fields (U.S. Department of Agricultural, 1983). In 1975, an estimated 0.1 million pounds were consumed in American fields (SRI, 1976).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

There are few data regarding the environmental fate and transport of isopropalin in water. Like other chemicals, the fate of isopropalin in water will depend on its ability to undergo chemical, photochemical and biological reactions and partition into the air or absorbed to sediments. Hydrolysis data for isopropalin are not available.

Photodegradation of isopropalin from soil surfaces has been known to occur (Section 2.3.); however, the rates of photodegradation or its products have not been developed. Therefore, while the photodecomposition of isopropalin in water is likely, its environmental significance is uncertain without further study. Similarly, isopropalin decomposition by microbial degradation in soil has been known to occur, but its environmental significance in the water is uncertain without further study.

The transport of isopropalin from water by volatilization has not been studied; however, its volatilization from soil surfaces has been examined (Section 2.3.). It has been noted that an increase in soil moisture content increases the rate of volatilization. Therefore, it is possible that the volatilization transport of isopropalin is a significant mechanism by which it is lost from the aquatic environment. The calculated Henry's Law Constant would also suggest that isopropalin will volatilize slowly from water (Lyman et al., 1982).

Isopropalin can be strongly adsorbed on soils (Section 2.3.). Therefore, it is likely that sorption to sediment in water is an important process. The high calculated K_{oc} value (Kenaga, 1980) also suggests sorption to sediments as an important transport process in water.

The bioaccumulation of isopropalin in edible tissues of bluegill sunfish has been examined using a flow-through system (Sleight, 1972). The fish were exposed to an isopropalin level of 0.01 ppm over a 28-day period. A moderate bioaccumulation occurred with rapid depuration; the maximum bioaccumulation factor for the edible tissue was 1600. Kenaga (1980) predicted BCFs bioconcentration factors for isopropalin, based upon water solubility and soil adsorption coefficient, to be 2150 and 7500, respectively. Compounds having a BCF >1000 have a strong potential to bioaccumulate.

The persistence of isopropalin in water has not been studied and cannot be predicted from the available data.

2.2. AIR

Data specific to the fate and transport of isopropalin in the atmosphere were not found in the available literature. As noted previously, photodegradation of isopropalin from soil surfaces has been known to occur (Section 2.3.); however, the rates of photodegradation or its products have not been developed. Therefore, while the photodecomposition of isopropalin in the atmosphere may occur, its environmental significance is uncertain without further study.

2.3. SOIL

The fate and transport of isopropalin in soil have been more adequately studied than its fate and transport in the air or in water. However, the predominant mechanism by which isopropalin is removed from the soil has yet to be determined conclusively. Microorganisms play a significant, but undefined, role in isopropalin disappearance from soil (U.S. EPA, 1981; WSSA, 1979).

Golab and Althaus, (1975) reported that isopropalin (unspecified formulation at 10 ppm) could not be detected 24 hours after addition to artificial rumen fluid incubated under anaerobic conditions. No degradation could

be demonstrated in sterilized preparations of rumen fluid. In addition, isopropalin was found to degrade slowly in submerged samples of nonsterilized soil in which only 27% of the applied isopropalin could be detected after 48 days. After 27 days in sterilized soil samples, no degradation of isopropalin was observed. Neither the microorganisms responsible for the isopropalin degradation nor the degradation products were identified.

Isopropalin that remains on the soil surface is subject to photodecomposition (WSSA, 1979). Parochetti and Dec (1978) applied ring-labeled ^{14}C -isopropalin at 1 ppm to thin-layer plates of Hagerstown clay loam soil and measured the effect of 7 days exposure to direct mid-July sunlight on photodegradation. The calculated photodecomposition loss for isopropalin under these conditions was 8.2% of the initial sample activity. Kennedy and Talbert (1977) found that the loss of isopropalin in methanol applied at 1 ppm to a silt loam soil averaged 19% after 24 hours exposure to an UV light (~310 nm), compared with a 5% loss of an identical sample in the dark at the same 45°C temperature.

Data specific to the chemical hydrolysis of isopropalin in soil are not available.

The transport of isopropalin (because of volatilization) from soil has been studied under laboratory conditions. Kennedy and Talbert (1977) found that volatilization of isopropalin increased slightly as moisture content was increased in a silt loam soil under UV light at 30°C. At 1 and 14% soil moisture content, 21% of applied isopropalin (1 ppm) was lost in 24 hours while at 26 and 33% soil moisture content, 28 and 29%, respectively, of applied isopropalin were lost. Partial loss of the isopropalin apparently

was due to photodecomposition. Parechetti et al. (1976) studied the volatilization of isopropalin for 3 hours following application to various soils and differing temperatures in a volatility chamber. In sandy soils, with a 7-15.3% moisture content, from 1-2.5% of applied isopropalin was volatilized within the 3 hours over a temperature range of 30-50°C; volatilization was lowest at 30°C. In Hagerstown clay loam (50°C), ~4% of applied isopropalin volatilized in 3 hours, while in Littleton silt loam ~3.5% volatilized in 3 hours. Harvey (1974) studied isopropalin volatility with a bioassay in which vapors from isopropalin-treated agar (1.0 μ M) inhibited foxtail millet growth to 14% of control growth.

The leachability of isopropalin in soils has been studied by a number of investigators, and their results indicate that isopropalin is relatively immobile in soil. Unpublished data (U.S. EPA, 1981) show that isopropalin remains in the top two inches of soil in soil leaching columns containing sandy soils and silt clay loam soils. Harvey (1974) studied the adsorption of isopropalin to a silt loam soil and found that it is strongly adsorbed. Kenaga (1980) determined an experimental K_{oc} for isopropalin to be 75,250 from data supplied in Harvey (1974). Kenaga (1980) also predicted a K_{oc} value, based on water solubility, for isopropalin to be 14,700. Compounds having a K_{oc} value of ≥ 1000 are quite tightly bound to organic matter in soil and are considered immobile.

Finally, the persistence of isopropalin in soils also has been studied by a number of investigators. Golab and Althaus (1975) removed the top 3 inches of a clay soil from field plots and mixed it with uniformly ring-labelled ^{14} C-isopropalin to yield 1.5 and 3.0 pounds isopropalin/acre. The treated soils were returned to the field, vegetable crops were planted and rotated with wheat, and the fate of the radioactivity and isopropalin in

the top 6 inches of soil was assessed over a 36-month period. The application rate was found to make little difference in the dissipation rate. Approximate persistence versus time is listed below:

<u>Time After Application</u>	<u>Percent of Applied Isopropalin Remaining</u>
1 month	81
2.5 months	61
4 months	57
6 months	55
12 months	37
15 months	25
24 months	18
36 months	7

Golab and Althaus (1975) identified 5 significant metabolites and 7 trace metabolites; the 5 major metabolites are as follows:

- (1) 2,6-dinitro-N-propylcumidine
- (2) 2,6-dinitrocumidine
- (3) 2-ethyl-5-isopropyl-7-nitro-1-propylbenzimidazole
- (4) 2-ethyl-5-isopropyl-7-nitrobenzimidazole
- (5) α,α -dimethyl-3,5-dinitro-4-dipropylaminobenzyl alcohol

Gingerich and Zimdahl (1976) determined aerobic and anaerobic rates of disappearance of isopropalin from a loam soil under laboratory conditions at 15°C and at 30°C. The aerobic half-lives at 15 and 30°C were 13.3 months and 3.5 months, respectively. The anaerobic half-lives at 15 and 30°C were 0.67 months and 0.17 months, respectively. Jacques and Harvey (1979) used an oat bioassay to determine the persistence of isopropalin in a silt loam soil under field conditions in 1974 and 1975. In both years, the initial isopropalin concentration of 1 ppm fell to ~0.25 ppm in ~85 days. Romanowski and Libik (1978) used a sorghum bioassay to determine the soil persistence of isopropalin in two soils in Indiana under field conditions

during 1972 at two rates of application (recommended and twice recommended). At both application rates, persistence in silt loam was ~135 days and persistence in fine sand was ~115 days. Stoller and Wax (1977), in a greenhouse study, found the half-life of isopropalin to be 4.3-9.9 months in silty loam clay and 5.8-6.4 months in silt loam. WSSA (1979) reported that isopropalin appears to degrade to nonphytotoxic levels during the growing season under warm, moist soil conditions.

U.S. EPA (1981) used available data to summarize the persistence of isopropalin as follows: isopropalin will not accumulate in silt loam and sandy clay loam soils and soils with a high sand content under normal field use conditions. Most of the applied isopropalin will remain in the 0- 3-inch soil layer, and very little, if any, will migrate below the 6-inch depth in most instances. In soils with a high sand content, isopropalin will likely exhibit a half-life of <2 months. Isopropalin tends to persist in loam and clay soils. The half-life of isopropalin in loam soils may range from 2-6 months.

3. EXPOSURE

3.1. WATER

The U.S. EPA STORET Data Base contains no listings or data for isopropalin. Other monitoring data for isopropalin in water were not found in the available literature. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

3.2. FOOD

Monitoring data for isopropalin exposure in food were not found in the available literature. Isopropalin is primarily used in tobacco fields. It is not significantly absorbed or translocated in crops planted in soils treated with isopropalin (WSSA, 1979). (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

3.3. INHALATION

Pertinent data regarding inhalation exposure to isopropalin were not located in the available literature.

3.4. DERMAL

Monitoring data for isopropalin exposure in the air or on the skin were not found in the available literature. As noted in Section 2.3., isopropalin is volatile under field conditions. For field workers, the greatest risk of exposure to isopropalin vapors are likely to be at the time of application and before soil incorporation.

4. PHARMACOKINETICS

Pertinent data regarding the adsorption, distribution, metabolism and excretion of isopropalin were not located in the available literature. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of isopropalin were not located in the available literature. This pesticide is not scheduled for testing by the National Toxicology Program (NTP, 1983). Isopropalin has been reported to be contaminated with a carcinogenic nitrosamine (Section 5.6.). (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

5.2. MUTAGENICITY

Pertinent data regarding the mutagenicity of isopropalin were not located in the available literature. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of isopropalin were not located in the available literature. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the reproductive effects of isopropalin were not located in the available literature. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

5.5. SUBCHRONIC AND CHRONIC TOXICITY

In an unpublished 90-day subchronic toxicity study, rats were fed technical grade isopropalin. The highest dose level was 0.225% isopropalin administered in the diet (2250 mg/kg) (Worth et al., 1969a). No pathologic

changes were associated with treatment (U.S. EPA, 1981). Dogs were fed encapsulated isopropalin daily at a dose of 56.25 mg/kg/day for 90 days. No pathological effects were described (WSSA, 1979). No further details were available for either of these subchronic studies.

5.6. OTHER RELEVANT INFORMATION

Data regarding the acute toxicity of isopropalin are summarized in Table 5-1.

Cohen et al. (1978) found 84-87 ppm of the N-nitrosamine, N-nitrosodipropylamine (NDPA), in isopropalin (emulsifiable concentrate), and Bontoyan et al. (1979) found 39-54 ppm of NDPA in isopropalin (emulsifiable concentrate). The manufacturer of isopropalin, Elanco, stated in 1980 that the contamination was <1 ppm in isopropalin (emulsifiable concentrate) but has not submitted data to support the statement (U.S. EPA, 1981). NDPA has caused hepatic, renal, esophageal and respiratory tract tumors in rats and hamsters (IARC, 1978).

TABLE 5-1
Acute Toxicity of Isopropalin

Species	Route	LD ₅₀ (mg/kg)	Reference
Mouse	oral	>5000 >2000	WSSA, 1979 U.S. EPA, 1981
Rat, adult or weanling	oral	5000	WSSA, 1979
Rat, adult	oral	>5000	U.S. EPA, 1981
Rat, newborn	oral	397	WSSA, 1979
Rabbit	oral	>2000	WSSA, 1979; U.S. EPA, 1981
Rabbit	dermal	>2000	U.S. EPA, 1981
Dog	oral	>2000	WSSA, 1979; U.S. EPA, 1981

6. AQUATIC TOXICITY

Data regarding the toxicity of isopropalin to aquatic species are limited to results of several unpublished manufacturer's reports (Elanco Products Co., Division of Eli Lilly and Company). Since these reports were not available for review, the results presented here are based on a brief summary by the U.S. EPA (1981). Toxicity tests were conducted in fathead minnows (Worth et al., 1969b) and goldfish (West and Worth, 1970), but effects or lethal levels were not given by the U.S. EPA (1981). It is evident from the toxicity tests, however, that isopropalin is highly toxic to warmwater fish.

Isopropalin was tested in bluegill sunfish for periods up to 42 days for its bioaccumulation potential (Sleight, 1972). Fish were exposed at 5 $\mu\text{g}/\text{L}$ (0.005 ppm) for 28 days with apparently no toxic effects. Tissue levels of isopropalin reached ~2-4 mg/kg during the exposure period and decreased to 0.61 and 0.04 mg/kg, respectively, 14 and 28 days after exposure was terminated. At an exposure level of 25 $\mu\text{g}/\text{L}$ (0.025 ppm) for 42 days, there were no reported toxic effects in fish. Levels in edible tissue reached 25-40 mg/kg during exposure and decreased to 9.0 and 1.07 mg/kg after 14 and 28 days postexposure. Therefore, BCFs of 800 and 1600, respectively, were reported for the body weight and high dose level.

Additional data regarding the toxicity of isopropalin to aquatic animals or plants were not located in the available literature. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

In 1972, a tolerance of 0.05 ppm isopropalin for tomatoes and bell peppers was established (U.S. EPA, 1981); however, currently, isopropalin is recommended for use only in growing tobacco. Therefore, the U.S. EPA (1981) has recommended the repeal of the tolerance established for food in 1972.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of isopropalin were not located in the available literature. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

8. RISK ASSESSMENT

Pertinent data regarding the carcinogenicity, mutagenicity, teratogenicity or chronic toxicity of isopropalin were not located in the available published literature as cited in the Appendix. Unpublished subchronic oral studies of the toxicity of isopropalin to rats and dogs were mentioned in secondary sources (U.S. EPA, 1981; WSSA, 1979), but were not reported in sufficient detail to support the derivation of an ADI.

Isopropalin is used almost exclusively as a preemergence herbicide on tobacco fields (see Section 1.4.). Because tobacco products are known to contain carcinogens regardless of pesticide use, the U.S. EPA is requiring only mutagenicity and teratogenicity studies, in addition to the already approved acute toxicity studies on isopropalin, to evaluate this pesticide (U.S. EPA, 1981).

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews the subchronic studies mentioned above in greater detail, providing a sufficient data base for quantitative risk assessment. An ADI of 0.056 mg/kg bw/day, or 3.9 mg/day for a 70 kg man, was derived based on a NOEL of 56.26 mg/kg bw/day in a subchronic feeding study using dogs and an uncertainty factor of 1000 (10 to

account for interspecies extrapolation, 10 for protection of the most sensitive individuals within the human population, and 10 for the use of a subchronic study for human ADI derivation). A dose of 75 mg/kg bw/day in rats was the LOAEL associated with reduced hemoglobin concentration and hematocrit.

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APPENDIX:
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

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